

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
19 July 2001 (19.07.2001)

PCT

(10) International Publication Number  
WO 01/51087 A2

- (51) International Patent Classification<sup>7</sup>: A61K 41/00
- (21) International Application Number: PCT/US01/00922
- (22) International Filing Date: 12 January 2001 (12.01.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/175,689 12 January 2000 (12.01.2000) US
- (71) Applicant (for all designated States except US): LIGHT SCIENCES CORPORATION [US/US]; 1065 12th Avenue, NW, No E-5, Issaquah, WA 98027 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): CHEN, James [US/US]; 2011 87th Place, NE, Bellevue, WA 98004 (US).
- (74) Agents: HOLLAND, Charles, D. et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/51087 A2

(54) Title: NOVEL TREATMENT FOR EYE DISEASE

(57) Abstract: This invention discloses methods, kits, and instructions to treat neovascular diseases of the eye through the administration of a targeted photosensitizing agent and subsequent exposure to light of specific wavelength sufficient to photoactivate photosensitizing agent. The photosensitizing agent is bound to a composition that mediates site specific delivery to a neovascular target tissue of a therapeutically effective amount of a photosensitizing agent that is activated by a relatively low fluence rate of light over a prolonged period of time. Diseases treatable under this invention, include: diabetic retinopathy; macular degeneration; and malignant uveal melanomas.

## NOVEL TREATMENT FOR EYE DISEASE

### TECHNICAL FIELD

5 This invention relates generally to the field of medicine and pharmacotherapeutics with photosensitizing agents or other energy activated agents. Specifically, this invention relates to kits and methods useful for the treatment of neovascular diseases of the eye. The invention involves the site specific delivery to a neovasculature target tissue of a therapeutically effective amount of a photosensitizing agent that is activated by a relatively low fluence rate of light over a prolonged period of time.

### BACKGROUND ART

10 Neovascular diseases of the eye include diabetic retinopathy, age-related macular degeneration and neovasculature growth induced by angiogenic factors or resulting from tumor cells, themselves. Diabetic retinopathy is characterized by a number and variety of microvascular changes which can result ultimately in adverse visual changes and vision loss. In many cases the microvascular changes are due to or associated with upregulation of angiogenesis receptors and factors or ligands which lead to new vessel formation, changes in vascular permeability, and possibly other alterations in vessel morphology. These changes may lead to hemorrhage, edema, ischemia, and other problems resulting in vision dysfunction (see: Aiello *et al.*, *Diabetes Care*, 21:143-156, 1998).

20 Treatments for the various forms of, and problems associated with, diabetic retinopathy include laser photocoagulation, vitrectomy, cryotherapy, and membranotomy. All of these clinical therapies and procedures are associated with problems and side effects. For example, the side effects and complications related to panretinal laser photocoagulation, the most common present treatment for diabetic retinopathy, include: decreased visual acuity, increased macular edema, transient pain, exudative retinal detachment, and inadvertent foveolar burns.

30 Age-related macular degeneration ("AMD") is the leading cause of blindness in the United States among individuals 65 or older. One form of AMD is characterized by formation of choroidal neovessels which can lead to a number of pathologic conditions resulting in visual dysfunction and loss. As with diabetic retinopathy, angiogenesis plays a key role in the formation of these neovessels. The proliferation of choroidal neovessels associated with AMD can contribute to irreversible damage of photoreceptors. Thus,

current treatment of AMD, like that of diabetic retinopathy, involves the use of laser photocoagulation. However, because photocoagulation relies upon the gross thermal destruction of the choroidal neovascular tissue, damage to the retina and surrounding choroidal tissue often results. Furthermore, recurrences after photocoagulation therapy are common. (see: Schmidt-Erfurth *et al.*, *Greafe's Arch Clin Exp Opthamol*, 236:365-374, 1998).

As an alternative to photocoagulation, photodynamic therapy has been proposed as a means of treating this form of AMD (see: Strong *et al.*, "Vision through photodynamic therapy of the eye," U.S. Patent Nos. 5,756,541 and 5,910,510; and Mori *et al.*, "Photochemotherapeutical obstruction of newly-formed blood vessels," U.S. Patent No. 5,6333,275). Photodynamic therapy ("PDT"), as taught in this prior art, is a two-step treatment process. PDT is performed by first administering a photosensitive compound systemically or topically, followed by illumination of the treatment site at a wavelength or waveband of light from a laser which closely matches the absorption spectra of the photosensitizer. In doing so, singlet oxygen and other reactive species are generated leading to a number of biological effects resulting in damage to the endothelial membranes and ultimately to clotting of the neovasculature.

Although this form of PDT represents an improvement over photocoagulation, clinical experience has established that the therapy must be repeated on a regular basis, typically every 3 months due to regrowth of the vessels (see: Schmidt-Erfurth *et al.*). The regrowth is believed to be due to upregulation of angiogenic factors and/or receptors secondary to the relative ischemia caused by the PDT treatment as outlined in the prior art. Clearly there is a need for a therapy which reduces the number of treatments which probably need to be performed for the rest of the patient's life.

In addition to neovascular tissue formation associated with diabetic retinopathy and age-related macular degeneration, the growth of new blood vessels are also associated with tumor formation in the eye, which results from two mechanisms: the stimulated growth of endothelial cells of existing blood vessels through angiogenesis; and a newly discovered vasculature resulting from highly malignant uveal melanomas, which develop in the eye, are full of networks of blood channels made by the melanoma cells themselves (Maniotis *et al.*, *American Journal of Pathology* 155(3): 739-52 (1999)). It may be that anti-angiogenic agents are ineffective in the treatment of such neovasculature arising not from endothelial cells, but from tumor cells such as those of malignant uveal melanomas.

Furthermore, because current PDT methods involve the systemic administration of untargeted photosensitive compounds or photosensitizers, the required dosages are relatively high which can lead to skin photosensitivity. The accumulation of photosensitizers in the skin is a property of all systemically administered sensitizers in clinical use. For example, clinically useful porphyrins such as Photophrin® (QLT, Ltd. brand of sodium porfimer) are associated with photosensitivity lasting up to 6 weeks. Purlytin®, which is a purpurin, and Foscan®, a chlorin, sensitize the skin for several weeks. Indeed, efforts have been made to develop photoprotectants to reduce skin photosensitivity (see: Dillon *et al.*, *Photochemistry and Photobiology*, 48(2): 235-238, 1988; and Sigdestad *et al.*, *British J. of Cancer*, 74:S89-S92, 1996). In fact, PDT protocols involving systemic administration of photosensitizer require that the patient avoid sunlight and bright indoor light to reduce the chance of skin phototoxic reactions.

While there are reports in the scientific literature describing the use of ligand-receptor binding pairs, that literature is primarily drawn to the treatment of malignant tumor cells. There are a few reports that address the treatment of eye-related neovascular diseases such as diabetic retinopathy and AMD. However, either these reports fail to disclose the use of PDT at all or these reports fail to teach the use of such methods in conjunction with the targeting of blood vessels (see, for example: Savitsky *et al.*, *SPIE*, 3191: 343-353, 1997; Ruebner *et al.*, *SPIE*, 2625: 328-332, 1996; Reno *et al.*, U.S. Pat. No. 5,630,996; Casalini *et al.*, *J. Nuclear Med.*, 38(9): 1378-1381, 1997; Griffiths, U.S. Pat. No. 5,482,698; and Mew *et al.*, *J. of Immunol.*, 130(3): 1473-1477, 1983). It should be noted that even though Strong *et al.* U.S. Patent Nos. 5,756,541 and 5,910,510 suggest that a photoactive agent may be coupled to a specific binding ligand which may bind to a specific surface component of the target ocular tissue, there is little guidance provided to suggest appropriate ligands effective in such PDT methods.

Regarding light sources for PDT, high powered lasers are usually employed in order to shorten the procedure time (see: Strong *et al.*, U.S. Patent Nos. 5,756,541 and 5,910,510; and Mori *et al.*, U.S. Patent No. 5,633,275; see more generally, W.G. Fisher, *et al.*, *Photochemistry and Photobiology*, 66(2):141-155, 1997).

However, the present art lacks an effective method of treating neovasculture diseases of the eye using a PDT methodology, which reduces damage to collateral or healthy tissue and which does not expose the tissue of the eye to intense laser light. The present art further teaches the need for recurrent treatment, the need for which is thought to

arise, as discussed above, due to upregulation of angiogenic factors and/or receptors secondary to the relative ischemia caused by the PDT treatment as outlined in the prior art. Clearly there is a need for a therapy which reduces the number of treatments which probably need to be performed for the rest of the patient's life.

5 Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents. Further, all documents referred to throughout this application are incorporated  
10 in their entirety by reference herein.

#### SUMMARY OF THE INVENTION

The present invention describes methods to treat neovascular disease of the eye based on the precise targeting of photosensitive compounds to target tissue and the activation of these targeted photosensitizer compounds by subsequently administering to  
15 the subject non-coherent (non-laser) or coherent (laser) light of a relatively low fluence rate over a prolonged period of time.

The present invention further discloses the selective binding of the photosensitizing agent to specific receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves bindable to endothelial receptors and  
20 antigens. This targeting scheme decreases the amount of sensitizing drug required for effective therapy, which in turn reduces the fluence rate or light irradiation needed for effective photoactivation. As a result, the disclosed method achieves maximal dosage to abnormal endothelium with minimal side effects or collateral tissue damage.

Additionally, the present disclosure teaches the unexpected use of a low power non-coherent light source utilized for longer than about 4 minutes. This teaches away from the  
25 use of a high powered, brief exposure using laser light, results in fuller, more efficient activation of the bound photosensitizers, and enables a high therapeutic index using a low dose drug. Moreover, a low power non-coherent light source is relatively inexpensive and simpler to use. Finally, because the present invention teaches photoactivation with a non-coherent, broadband light source, different types of photosensitizers can be activated with a  
30 single light source.

Due to the highly specific nature of the photosensitizer uptake, excess light or light falling on nonpathologic areas causes no unwanted photoactivation. Therefore, a region of

the retina or macular with diffuse abnormalities can be safely treated without damaging intervening normal eye structures. In addition, eye movement by the patient during treatment, which can result in the further exposure to light of normal eye structures, is harmless. Thus, the use of highly targeted photosensitizers allows the delivery of light in a diffuse fashion and over a prolonged illumination period. In fact, one embodiment of the invention is the use of ambient light to activate the photosensitized neovascular tissue.

Further, the binding of the photosensitizer/ligand conjugate to the endothelial receptor, as taught by the present invention, causes blockage and/or down regulation of the receptor which further inhibits neovessel formation and subsequent regrowth of neovasculature, which generally results from more traditional methods of PDT. Similarly, the use of a photosensitizer/receptor conjugate would serve to bind circulating ligands also inhibiting neovessel formation. This added benefit of the present invention operates independently of the light-activated vessel occlusion described above.

An embodiment of the present invention is drawn to a method for photodynamic therapy ("PDT") of neovascular disease of the eye comprising: administering to the subject a therapeutically effective amount of a photosensitizing compound, where the photosensitizing compound selectively binds to the target abnormal endothelium that lines or composes the neovasculature target tissue. This step is followed by illuminating the neovasculature tissue with light at a wavelength or waveband absorbed by the targeted photosensitizing compound where the light is provided by a non-laser light source, and for a period of time sufficient to activate the photosensitizing compound thereby causing damage to the neovasculature target tissue. In this embodiment of the present invention, the targeted photosensitizing compound is cleared from non-target tissues of the subject prior to irradiation.

A preferred embodiment of the present invention is drawn to a method for PDT of neovascular disease of the eye as described above, wherein the neovascular target tissue is present in the retina, choroid or both of a subject diagnosed with diabetic retinopathy or age-related macular degeneration ("AMD"). A further preferred embodiment of this invention provides a method for PDT of neovascular tissue associated with tumor formation in the eye, and more specifically neovascular tissue resulting from angiogenesis or growth factors elicited by tumors, such as malignant uveal melanomas.

A more preferred embodiment of the present invention is drawn to a method of PDT of neovascular disease of the eye as described above, wherein the targeted photosensitizing

compound is bound to a first component of a bindable pair and wherein the second component of the bindable pair is selected from the group consisting of: receptor present on abnormal endothelium; ligand bindable to receptor present on abnormal endothelium; antigen present on abnormal endothelium; and antibody bindable to antigen present on abnormal endothelium.

Yet another preferred embodiment contemplates a method of PDT of neovascular disease of the eye as described above, where the ligand is selected from the group consisting of: VEGF; VEGF receptor; and  $\alpha$ -3,  $\beta$ -3 integrin receptor. A further preferred embodiment provides a method of PDT of neovascular disease of the eye, where the ligand comprises an antibody specific or having a high degree of affinity for the extra-domain B (or ED-B) of fibronectin. An even more preferred embodiment is drawn to the ligand discussed above, which is a complete or functional bindable fragment of a human antibody, such as L19 or its equivalent (see: Birchler *et al.*, *Selective targeting and photocoagulation of ocular angiogenesis mediated by a phage-derived human antibody fragment*, *Nature Biotech.* 17: 984 (1999)).

Another preferred embodiment of the present invention is drawn to a method of PDT of neovascular disease of the eye as described above, where the targeted photosensitizing compound is bound to a receptor composition that mimics a receptor present on abnormal endothelium.

Another preferred embodiment of the present invention is drawn to a method of PDT of neovascular disease of the eye as described above, where the targeted photosensitizing compound is bound to a bi-specific antibody construct that further comprises both a ligand component and a receptor component.

A still further embodiment of the present invention is drawn to a method of PDT of neovascular disease of the eye as described above, where the targeted and bound photosensitizing compound is incorporated into a liposomal preparation.

The invention also provides kits comprising any of the components that are used in PDT of neovascular disease as taught herein and instructions (such as an instruction sheet or computer disk) that teach the methods described herein.

The invention also provides methods of teaching a person to conduct treatments of neovascular disease, where the methods comprise instructing a person to conduct the PDT methods described herein.

### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates three types of bound photosensitizing compounds: ligand construct, receptor construct, and bispecific antibody construct.

5 Figure 2 illustrates a photosensitizing compound incorporated into a liposomal preparation that includes a ligand construct, receptor construct, and bispecific antibody construct.

Figure 3 shows an eye subjected to ambient light and collimated LED light.

Figure 4 shows a lateral view of skull (partial) with placement of LED light sources.

10

### DETAILED DESCRIPTION OF THE INVENTION

This invention provides methods for treating neovascular disease of the eye by the specific and selective binding of a photosensitizing compound to the abnormal endothelium that lines or composes the neovasculature target tissue. This method comprises illuminating the photosensitized target tissue with light for a period of time sufficient to  
15 activate the bound photosensitizing compound thereby causing damage to the neovasculature target tissue.

Specifically, the present invention is based on the precise targeting of photosensitizing compounds to specific target receptors and/or antigens present on abnormal endothelium or to specific ligands and/or antibodies which are themselves  
20 bindable to endothelial receptors and antigens, and to the method of activation of the bound and targeted photosensitizing compounds by subsequently administering to the target tissue light of a relatively low fluence rate over a prolonged period of time. The disclosed method achieves maximal damage to abnormal endothelium with minimal side effects or collateral tissue damage.

25 Terms as used herein are based upon their art recognized meaning and from the present disclosure should be clearly understood by the ordinary skilled artisan. For sake of clarity, terms may also have particular meaning as would be clear from their use in context.

Further, as used herein, "target tissues" are those tissues that are intended to be impaired or destroyed by this treatment method. Photosensitizing compounds bind to these  
30 target tissues; then when sufficient radiation is applied, these tissues are impaired or destroyed.

"Non-target tissues" are all the tissues of the eye which are not intended to be impaired or destroyed by the treatment method. These non-target tissues include but are not



limited to healthy blood cells, and other normal tissue of the retina and choroid, not otherwise identified to be targeted.

5 "Photosensitizing compound" is a chemical compound which homes to one or more types of selected target cells and, when contacted by radiation, absorbs the light, which results in impairment or destruction of the target cells. Virtually any chemical compound that homes to a selected target and absorbs light may be used in this invention. Preferably, the chemical compound is nontoxic to the subject to which it is administered or is capable of being formulated in a nontoxic composition. Preferably, the chemical compound in its photodegraded form is also nontoxic. A comprehensive listing of photosensitive chemicals may be found in Kreimer-Birnbaum, Sem. Hematol. 26:157-73, 1989. Photosensitive compounds include, but are not limited to, chlorins, bacteriochlorophylls, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD) and porfimer sodium and pro-drugs such as  $\delta$ -aminolevulinic acid, which can produce drugs such as protoporphyrin. Other compounds include indocyanine green (ICG); methylene blue; toluidine blue; texaphyrins; and any other agent that absorbs light in a range of 500 nm -1100 nm.

15 "Illumination" as used herein includes all wave lengths and wavebands. Preferably, the illumination wave length or waveband is selected to match the wave length(s) or wavebands which excite the photosensitive compound. Even more preferably, the radiation wave length or waveband matches the excitation wave length or waveband of the photosensitive compound and has low absorption by the non-target tissues of the eye, and the rest of the subject, including blood proteins.

20 The irradiation by illumination is further defined in this invention by its coherence (laser) or non-coherence (non-laser), as well as intensity, duration, and timing with respect to dosing using the photosensitizing compound. The intensity or fluence rate must be sufficient for the light to reach the target tissue. The duration or total fluence dose must be sufficient to photoactivate enough photosensitizing compound to act on the neovasculature target tissue. Both intensity and duration must be limited to avoid overtreating the subject. Timing with respect to dosing with the photosensitizing compound is important, because 1) 25 the administered photosensitizing compound requires some time to home in on neovasculature target tissue and 2) the blood level of many photosensitizing compounds decreases with time.

Briefly, the photosensitizing compound is generally administered to the subject before the neovasculature target tissue is subjected to illumination.

Preferred photosensitizing compounds include, but are not limited to, chlorins, bacteriochlorophylls, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens and pro-drugs such as  $\delta$ -aminolevulinic acid, which can produce drugs such as protoporphyrin. More preferred are: methylene blue; toluidine blue; texaphyrins; and any other agent that absorbs light in a range of 600 nm -1100 nm. Most preferred is indocyanine green (for example, see: WO 92/00106 (Raven *et al.*); WO97/31582 (Abels *et al.*) and Devoisselle *et al.*, *SPIE* 2627:100-108, 1995). Additional photosensitizing compounds, include: pyropheophorbide compounds (see: U.S. Patent No.: 5,459,159); bacteriochlorophyll derivatives (see: U.S. Patent No.: 5,955,585); and Alkyl ether analogs of chlorins (see: U.S. Patent No.: 5,952,366).

Any one or combination of these or other photosensitizing compounds may be supplied in a kit of this invention along with instructions on conducting any of the methods disclosed herein. Instructions may be in any tangible form, such as printed paper, a computer disk that instructs a person how to conduct the method, a video cassette containing instructions on how to conduct the method, or computer memory that receives data from a remote location and illustrates or otherwise provides the instructions to a person (such as over the Internet). A person may be instructed in how to use the kit using any of the instructions above or by receiving instructions in a classroom or in the course of treating a patient using any of the methods disclosed herein, for example.

The photosensitizing compound is administered orally, intravenously by injection, or via the intraocular route. The photosensitizing compound can be conjugated to various antibodies, antibody fragments, and other molecules and compounds capable of binding to the endothelium of neovessels. The specific ligands reactive with the target endothelium include antibodies and antibody fragments that bind to abnormal or upregulated vascular endothelial receptors such as the VEGF receptors and  $\alpha$ -3,  $\beta$ -3 integrins (see: Ferrara, *Curr Top Microbiol Immunol*, 237:1-30, 1999; Elicieri and Cheresch. *The Journal of Clinical Investigation*, 103:1227-30, 1999; Smith *et al.*, *Br J Ophthalmol*. 83:486-494, 1999). Also, the antibody can be drawn to and have affinity to bind to the extra-domain B (or ED-B) of fibronectin. Such antibodies, include a complete or functional bindable fragment of a human antibody, such as L19 or its equivalent (see: Birchler *et al.*, *Selective targeting and photocoagulation of ocular angiogenesis mediated by a phage-derived human antibody*

*fragment, Nature Biotech.* 17: 984 (1999)). The ligand can be any molecule or compound that binds to a endothelial receptor found on an abnormal blood vessel wall. Preferably the ligand binds selectively to receptors which are mainly or only found on the abnormal blood vessel wall.

5 Another embodiment of the present invention involves the use of a photosensitizing compound bound to a receptor-type molecule or compound. The receptor mimics the type of receptors found on the endothelium of abnormal vessel walls. Preferably the receptor mimic binds ligands, such VEGF, that are found to be elevated in concentration or are not normally present due to the abnormal conditions relating to the abnormal blood vessel formation. An additional embodiment involves the use of a bispecific antibody construct  
10 that is a combination ligand and receptor type molecule or compound that is bound to a photosensitizing compound. The bispecific nature of this construct allows binding of either an abnormal endothelial receptor or an abnormal ligand or abnormally elevated concentration of ligand.

15 Alternatively, the photosensitizing compound can be packaged into liposomes and the ligand, receptor, or bispecific construct incorporated or attached to the liposome to serve as a further means of targeting. In each of the above embodiments, preferably more than one photosensitizing compound is attached to the targeting moiety.

The technique of constructing bispecific antibodies, the techniques and methods of  
20 linking photosensitizers to targeting agents, and the techniques of producing targeted liposomes are well known in the art. For example, useful reviews of such techniques are provided by Yatvin *et al.*, U.S. Patent No. 5,827,819 (1998) and Jansen, *et al.*, U.S. Patent No. 5,869,457 (1999).

The bound photosensitizing compound can be administered in a dry formulation,  
25 such as pills, capsules, suppositories or patches. The compound also may be administered in a liquid formulation, either alone with water, or with pharmaceutically acceptable excipients, such as are disclosed in Remington's Pharmaceutical Sciences. The liquid formulation also can be a suspension or an emulsion. In particular, liposomal or lipophilic formulations are desirable. If suspensions or emulsions are utilized, suitable excipients  
30 include water, saline, dextrose, glycerol, and the like. These compositions may contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, antioxidants, pH buffering agents, and the like.

The dose of photosensitizing compound can be determined clinically and will be the lowest dose that saturates the available binding sites. Depending on the photosensitizing compound used, an equivalent optimal therapeutic level will have to be established. A certain length of time is allowed to pass for the circulating or locally delivered photosensitizer to be taken up by the endothelium of the neovessels. The unbound photosensitizer is cleared from the circulation during this waiting period. The waiting period will be determined clinically and may vary from compound to compound.

At the conclusion of this waiting period, a non-laser light source is used to activate the bound drug, although a laser light source may be used. The spot size illuminating the retina or choroid is determined by the location and dimension of the pathologic region to be treated. The duration of illumination period will be determined empirically, but is preferably a total or cumulative period of time between about 4 minutes and 72 hours. More preferably, the illumination period is between about 60 minutes and 148 hours. Most preferably, the illumination period is between about 2 hrs and 24 hours.

Preferably, the total fluence or energy of the light used for irradiating, as measured in Joules, is between about 30 Joules and about 25,000 Joules; more preferably, between about 100 Joules and about 20,000 Joules; and most preferably, between about 500 Joules and about 10,000 Joules. Light having a waveband corresponding at least in part with the characteristic light absorption waveband of said photosensitizing agent is used for irradiating the target tissue.

The intensity or power of the light used is measured in watts, with each Joule equal to one watt-sec. Therefore, the intensity of the light used for irradiating in the present invention may be substantially less than  $500 \text{ mW/cm}^2$ . Since the total fluence or amount of energy of the light in Joules is divided by the duration of total exposure time in seconds, the longer the amount of time the target is exposed to the irradiation, the greater the amount of total energy or fluence may be used without increasing the amount of the intensity of the light used. The present invention employs an amount of total fluence of irradiation that is sufficiently high to activate the photosensitizing agent, as applicable, with a concomitant reduction in the intensity of light and collateral or non-target specific tissue damage.

While not wishing to be limited by a theory, the inventor proposes that a targeted photosensitizing compound can be substantially and selectively photoactivated in the neovasculature target tissue within a therapeutically reasonable period of time and without excess toxicity or collateral damage to non-target tissues. A relatively low fluence can be

used for a relatively long period of time in order to fully photoactivate the drug in order to insure adequate closure of the neovessels and vessel abnormalities.

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

### EXAMPLES

#### EXAMPLE 1      TREATMENT OF CHOROIDAL NEOVASCULATURE LESIONS

A subject with choroidal neovascularization (CNV) from age-related macular generation is assessed using standard visual acuity testing, ophthalmic examination, color photographs and fluorescein angiograms (see Miller *et al.*, *Ach. Ophthal.* vol. 117:1161-1173 (1999)).

A photosensitizing agent, verteporfin, is conjugated using generally recognized methods in the art to a bindable fragment of the L19 antibody demonstrating high affinity to the ED-B of fibronectin (Birchler *et al.*, *Nature Biotech.* 17: 984 (1999)). A therapeutically effective amount of the photosensitizing agent conjugate, approximately 5 mg/m<sup>2</sup>, is administered intravenously to the subject.

Following a period of approximately 1 hour, to permit the non-specifically bound photosensitizing agent conjugate to clear from collateral tissues, the subject is irradiated in one or more sessions for a total period of 10 minutes with 400 mW/cm<sup>2</sup> of collimated LED light having a wavelength of 690 nm. This represents a total fluence of 240 Joules/cm<sup>2</sup>.

The entire lesion is treated with a single spot of the size as determined from a pretreatment angiogram. A margin of 300-500 µm may be added to ensure complete coverage of the lesion. A green non-activating observation light beam may be used for real-time observation and aiming during PDT.

Screening examinations may be performed during the first week immediately before treatment. Visual acuity is measured by standard refraction protocol using EDTRS criteria. A slit-lamp and a complete ophthalmoscopic exam is performed. Optic discs and maculae of both eyes are documented by stereo color photography. Stereo fluorescein angiography is performed with 10% sodium fluorescein. Frames are taken according to MPS standards. The photodynamic effects are monitored after 1, 4, and 12 weeks by means of visual acuity, ophthalmoscopy, fundus photography and stereo angiography. Angiograms are evaluated for angiographic occlusion and leakage after PDT.

### EXAMPLE 2      TREATMENT OF RETINAL NEOVASCULATURE LESIONS

According to Example 1, a liposomal benzoporphyrin derivative is conjugated to VEGF for use as a photosensitizer. A drug dose of  $10 \text{ mg/m}^2$  is administered to a subject with neovascular lesions in the retina of the eye via intravenous infusion over 10 minutes. The subject waits for a period of 6 hours to permit clearance from the tissues of non-specifically bound photosensitizing conjugate before illumination therapy is administered.

With the photosensitizer specifically localized to the retinal neovasculture lesions comprising VEGF receptor on the surface of the cells of the lesion, the subject is exposed to non-coherent light from a low power non-coherent broadband light source emitting at 690 nm. This illumination provides a radiant exposure of no more than  $500 \text{ mW/cm}^2$  for a period of approximately 20 minutes in one or more sessions producing a total fluence of illumination of about  $600 \text{ Joules/cm}^2$ . Alternatively, coherent or laser light could be similarly employed. Photosensitization is performed with dilated pupils and topical anesthesia using a contact lens.

The entire lesion is treated with a single spot of the size as determined from a pretreatment angiogram. A margin of  $300\text{-}500 \mu\text{m}$  is added to ensure complete coverage of the lesion. A green non-activating observation light beam is used for real-time observation and aiming during PDT. Screening examinations and visual acuity as disclosed in Example 1 is performed.

### EXAMPLE 3      TREATMENT OF VASCULAR TUMORS OF THE EYE

Integrin  $\alpha\text{v}\beta 3$  integrin is expressed by vascular cells during angiogenesis and vascular remodeling and is highly expressed by endothelial cells undergoing angiogenesis in tumors. See Eliceiri, B. P. *et al.*, J. Clin. Invest (1999) 103(9):1227-1230. Antibody elicited to  $\alpha\text{v}\beta 3$ , such as LM609 (Vitaxin; Eliceiri *et al.*) is conjugated to a texaphyrin photosensitizing agent in a liposomal formulation. A drug dose of  $25 \text{ mg/m}^2$  is administered via intravenous infusion over 10 min. The photosensitizer localizes to the neovasculture lesions. The pupils are dilated to allow ambient light enter for photosensitization. Therefore, no slit lamp is needed for photosensitization and the subject may continue everyday activities while receiving PDT. The ambient light is used to photoactivate the photosensitizing agent for a total exposure time of 24 hours.

Screening examinations and visual acuity as disclosed in Example 1 is performed.

EXAMPLE 4      TREATMENT CHOROIDAL TUMOR OF THE EYE

Most ocular tumors metastasize from systemic origins in breast carcinoma in females, and bronchial carcinoma in males (Chen YR, et al., *Bilateral choroidal metastases as the initial presentation of a small breast carcinoma: a case report*, Chung Hua I Hsueh Tsa Chih (Taipei); 61(2):99-103 1998). Antibody elicited to carcinoembryonic antigen (CEA), which is associated with the choroidal tumor, is conjugated to a benzoporphyrin derivative photosensitizing agent in a liposomal formulation. A drug dose of 10 mg/m<sup>2</sup> is administered via intravenous infusion over 10 min.

Additionally, the patient is administered the anti- $\alpha v \beta 3$  antibody-texaphyrin conjugate at a drug dose of 25 mg/m<sup>2</sup> as provided in Example 3.

After the texaphyrin photosensitizer conjugate localizes to the neovasculature lesion and the benzoporphyrin-anti-CEA conjugate localizes to the CEA tumor antigens, a period of 6 hours is permitted to pass to permit the unbound or non-specifically bound photosensitizer conjugates to clear from the lesions.

A low power non-coherent broadband light source emitting at 690 nm is used as described in Example 2. The radiant exposure of 250 mW/cm<sup>2</sup> is employed for approximately 1 hour over the course of one or more sessions to provide a total fluence of 900 J/cm<sup>2</sup>. Photosensitization is performed with dilated pupils and topical anesthesia using a contact lens. The entire lesion is treated with a single spot of the size as determined from a pretreatment angiogram. A margin of 300-500  $\mu$ m is added to ensure complete coverage of the lesion. A green non-activating observation light beam is used for real-time observation and aiming during PDT. Screening examinations and visual acuity as disclosed in Example 1 is performed.

Although the present invention has been described in connection with the preferred form of practicing it, those of ordinary skill in the art will understand that many modifications can be made thereto within the scope of the claims that follow. Accordingly, it is not intended that the scope of the invention in any way be limited by the above description, but instead be determined entirely by reference to the claims that follow.

CLAIMS

The invention claimed is:

1. A method to treat neovascular disease of the eye, comprising:
  - 5 administering a targeted photosensitizing compound which selectively binds to abnormal endothelium that lines or composes neovasculature tissue; and
  - illuminating the neovasculature tissue with light for a period of time sufficient to activate the photosensitizing compound thereby causing damage to neovasculature tissue.
- 10 2. The method of claim 1, wherein said light is non-laser light.
3. The method of claim 1, wherein said light is laser light.
4. The method of claim 1, wherein the neovasculature tissue is present in retina, choroid or both.
- 15 5. The method of claim 1, wherein the treated neovascular disease is diabetic retinopathy.
6. The method of claim 1, wherein the treated neovascular disease is macular degeneration.
7. The method of claim 1, wherein the treated neovascular tissue arises from tumors of the eye.
- 20 8. The method of claim 1, wherein said tumors are benign.
9. The method of claim 1, wherein said tumors are malignant.
10. The method of claim 9, wherein said tumors are malignant uveal melanomas.
11. The method of claim 1, wherein the targeted photosensitizing compound is bound to a first component of a bindable pair and wherein a second component of the bindable pair is selected from the group consisting of: receptor present on abnormal endothelium; ligand bindable to receptor present on abnormal endothelium; antigen present on abnormal endothelium; and antibody bindable to antigen present on abnormal endothelium.
- 25 12. The method of claim 11, wherein the targeted photosensitizing compound is incorporated into a liposomal preparation.
- 30 13. The method of claim 11, wherein the ligand is selected from the group consisting of: the ED-B domain of fibronectin; antibody specifically elicited to ED-B domain of fibronectin; VEGF; VEGF receptor; and  $\alpha v \beta 3$  integrin receptor.



14. The method of claim 1, wherein the targeted photosensitizing compound is bound to a receptor composition that mimics a receptor present on abnormal endothelium.
- 5 15. The method of claim 14, wherein the targeted photosensitizing compound is incorporated into a liposomal preparation.
16. The method of claim 1, wherein the targeted photosensitizing compound is bound to a bi-specific antibody construct that further comprises both a ligand component and a receptor component.
- 10 17. The method of claim 16, wherein the targeted photosensitizing compound is incorporated into a liposomal preparation.
18. The method of claim 1, wherein the photosensitized neovasculature is illuminated for at least 4 minutes.
19. The method of claim 1, wherein the photosensitized neovasculature is illuminated for at least 20 minutes.
- 15 20. The method of claim 1, wherein the photosensitized neovasculature is illuminated for at least 1 hour.
21. The method of claim 1, wherein the photosensitized neovasculature is illuminated for at least 24 hours.
- 20 22. The method of claim 1, wherein the neovasculature tissue is treated with a total fluence of light irradiation from between about 240 J/cm<sup>2</sup> to about 900 J/cm<sup>2</sup>.
23. The method of claim 1, wherein the non-laser light source is a light emitting diode.
24. The method of claim 1, wherein the non-laser light source is ambient light.
25. A method to treat neovascular disease of the eye, comprising:
- 25 administering a first targeted photosensitizing compound which selectively binds to a first targeted tissue; and
- administering a second targeted photosensitizing compound which selectively binds to a second targeted tissue; and
- 30 illuminating the first and second targeted tissues with non-laser light for a period of time sufficient to activate said first and second photosensitizing compounds thereby causing damage to said first and second targeted tissue.
26. The method of claim 25, wherein said first targeted tissues is abnormal endothelium that lines or composes neovasculature tissue; and said second targeted tissue is a tumor antigen.

27. The method of claim 26, wherein said first targeted photosensitizing compound comprises a ligand selected from the group consisting of: the ED-B domain of fibronectin; antibody specifically elicited to ED-B domain of fibronectin; VEGF; VEGF receptor; and  $\alpha v \beta 3$  integrin receptor.
- 5 28. A kit to treat neovascular disease of the eye, comprising a targeted photosensitizing compound and instructions teaching a method according to any of claims 1-27.
- 10 29. A kit according to claim 28 wherein the targeted photosensitizing compound binds to a first component of a bindable pair and wherein a second component of the bindable pair is selected from the group consisting of: receptor present on abnormal endothelium; ligand bindable to receptor present on abnormal endothelium; antigen present on abnormal endothelium; and antibody bindable to antigen present on abnormal endothelium.
- 15 30. A kit according to claim 29, wherein the targeted photosensitizing compound is incorporated into a liposomal preparation.
31. A kit according to claim 29, wherein the ligand is selected from the group consisting of: the ED-B domain of fibronectin; antibody specifically elicited to ED-B domain of fibronectin; VEGF; VEGF receptor; and  $\alpha v \beta 3$  integrin receptor.
- 20 32. A kit according to claim 28, wherein the targeted photosensitizing compound binds to a receptor composition that mimics a receptor present on abnormal endothelium.
33. A kit according to claim 32, wherein the targeted photosensitizing compound is incorporated into a liposomal preparation.
- 25 34. A kit according to claim 28, wherein the targeted photosensitizing compound binds to a bi-specific antibody construct that further comprises both a ligand component and a receptor component.
35. A kit according to claim 34, wherein the targeted photosensitizing compound is incorporated into a liposomal preparation.
- 30 36. A method of instructing a person to treat neovascular disease of the eye, comprising instructing a person to conduct a method according to any of claims 1-27.
37. A method of instructing a person to treat neovascular disease of the eye, comprising instructing a person in the use of a kit of any of claims 28-35.

1/2

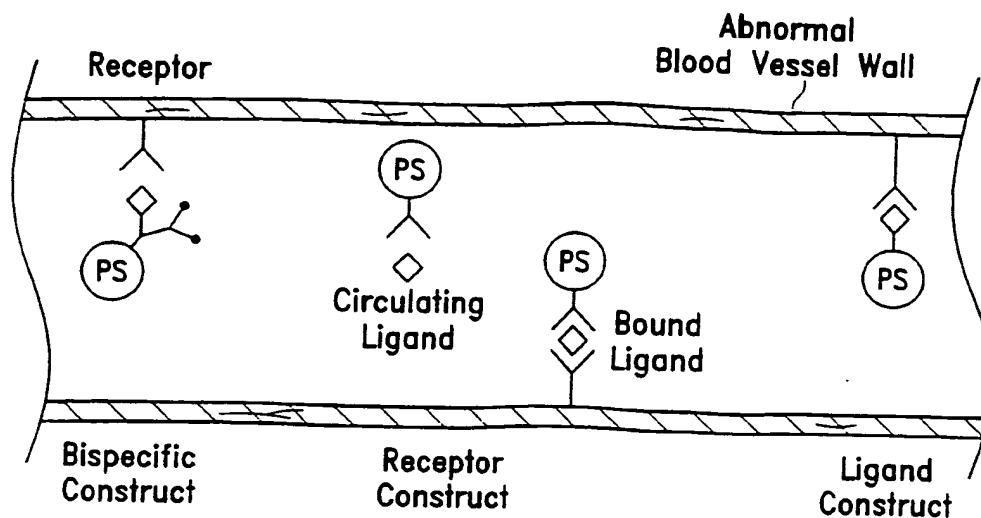


FIG. 1

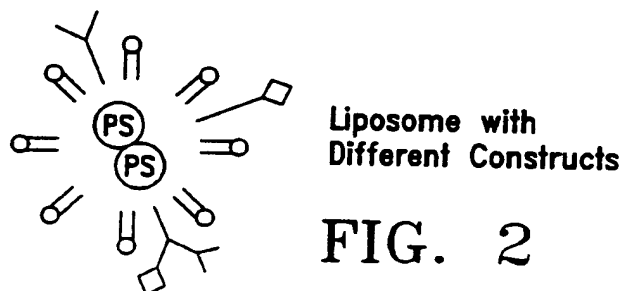
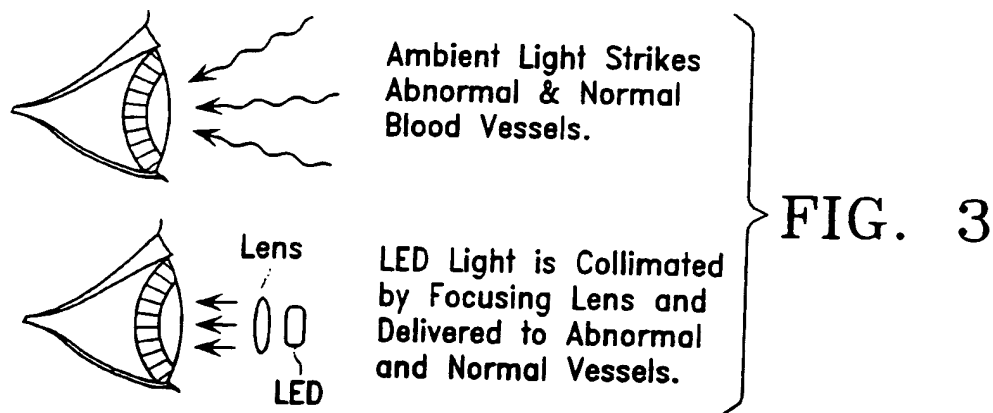
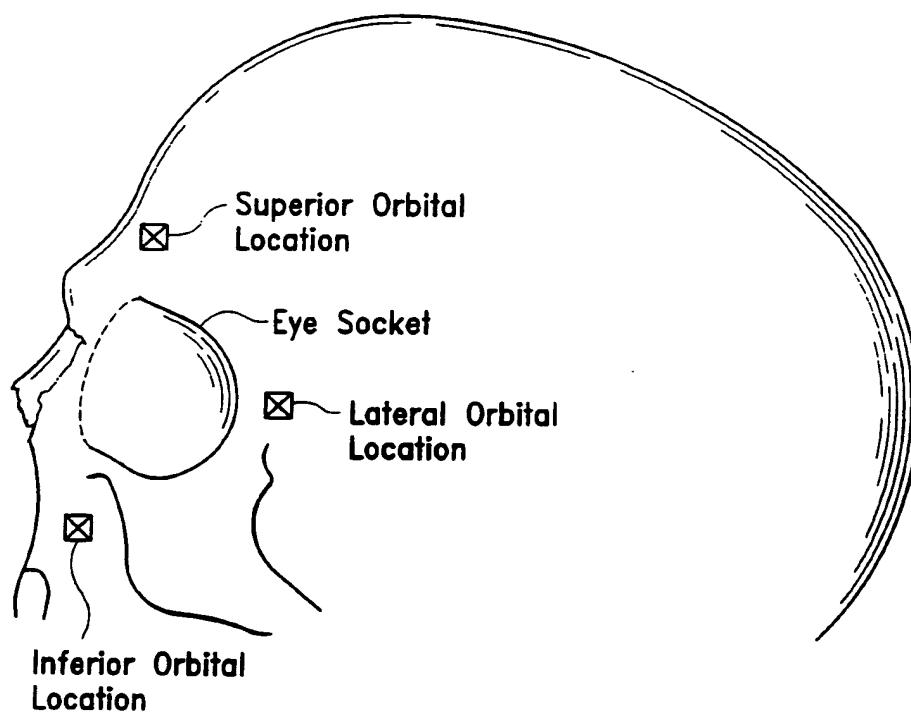


FIG. 2



2/2



- ☒ LED Light Source.  
The Light is Delivered transcutaneously through  
the Skin, Soft Tissue and Orbital Walls.

FIG. 4

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
19 July 2001 (19.07.2001)

PCT

(10) International Publication Number  
**WO 01/51087 A3**

(51) International Patent Classification: **A61K 47/48**,  
41/00

(21) International Application Number: **PCT/US01/00922**

(22) International Filing Date: 12 January 2001 (12.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/175,689 12 January 2000 (12.01.2000) US

(71) Applicant (for all designated States except US): **LIGHT SCIENCES CORPORATION** [US/US]; 1065 12th Avenue, NW, No E-5, Issaquah, WA 98027 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **CHEN, James** [US/US]; 2011 87th Place, NE, Bellevue, WA 98004 (US).

(74) Agents: **HOLLAND, Charles, D. et al.**; Morrison & Foster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR). OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:  
10 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/51087 A3

(54) Title: **NOVEL TREATMENT FOR EYE DISEASE**

(57) Abstract: This invention discloses methods, kits, and instructions to treat neovascular diseases of the eye through the administration of a targeted photosensitizing agent and subsequent exposure to light of specific wavelength sufficient to photoactivate photosensitizing agent. The photosensitizing agent is bound to a composition that mediates site specific delivery to a neovascular target tissue of a therapeutically effective amount of a photosensitizing agent that is activated by a relatively low fluence rate of light over a prolonged period of time. Diseases treatable under this invention, include: diabetic retinopathy; macular degeneration; and malignant uveal melanomas.

# INTERNATIONAL SEARCH REPORT

International Application No  
PC1/US 01/00922

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K47/48 A61K41/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)  
BIOSIS, EPO-Internal, MEDLINE, CANCERLIT, DISSERTATION ABS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHMIDT-ERFURTH URSULA ET AL: "Vascular targeting in photodynamic occlusion of subretinal vessels." OPHTHALMOLOGY, vol. 101, no. 12, 1994, pages 1953-1961, XP001052873 ISSN: 0161-6420 abstract page 1954, left-hand column, last paragraph -page 1955, left-hand column, line 2 page 1959, paragraph DISCUSSION -page 1960 --- -/--	1-37

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*3\* document member of the same patent family

Date of the actual completion of the international search

16 January 2002

Date of mailing of the international search report

04/02/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax (+31-70) 340-3016

Authorized officer

Dullaart, A

## INTERNATIONAL SEARCH REPORT

International Application No  
PC1/US 01/00922

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHMIDT-ERFURTH U ET AL: "IN VIVO UPTAKE OF LIPOSOMAL BENZOPORPHYRIN DERIVATIVE AND PHOTOTHROMBOSIS IN EXPERIMENTAL CORNEAL NEOVASCULARIZATION" LASERS IN SURGERY AND MEDICINE, WILEY-LISS, NEW YORK, US, vol. 17, 1995, pages 178-188, XP000764070 ISSN: 0196-8092 abstract page 179, right-hand column, last paragraph -page 180, left-hand column, line 2 page 181, right-hand column, last paragraph -page 182, left-hand column page 185, right-hand column, last line -page 186, left-hand column ---	1-37
X	BIRCHLER M ET AL: "SELECTIVE TARGETING AND PHOTOCOAGULATION OF OCULAR ANGIOGENESIS MEDIATED BY A PHAGE-DERIVED HUMAN ANTIBODY FRAGMENT" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 17, October 1999 (1999-10), pages 984-988, XP001013718 ISSN: 1087-0156 abstract page 984, paragraph RESULTS -page 986, left-hand column, line 8 ---	1-37
X	WO 96 06641 A (PRIZM PHARMA INC) 7 March 1996 (1996-03-07) page 17, line 1 - line 29 page 22, line 24 -page 23, line 2 ---	1-37
X	SCHMIDT-ERFURTH U ET AL: "Photodynamic therapy of experimental choroidal melanoma using lipoprotein-delivered benzoporphyrin." OPHTHALMOLOGY, JAN 1994, VOL. 101, NO. 1, PAGE(S) 89-99, XP001052874 abstract page 95, paragraph DISCUSSION -page 98 ---	1-37
Y	US 5 929 105 A (DOLPHIN DAVID ET AL) 27 July 1999 (1999-07-27) example 9 ---	1-37
Y	US 5 798 349 A (LEVY JULIA ET AL) 25 August 1998 (1998-08-25) examples ---	1-37
	---	
	-/--	

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/00922

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	WO 98 50387 A (QLT PHOTOTHERAPEUTICS INC ;UNIV BRITISH COLUMBIA (CA)) 12 November 1998 (1998-11-12) examples 9,13 ---	1-37
Y	JIANG HUIJUN ET AL: "Selective depletion of a thymocyte subset in vitro with an immunomodulatory photosensitizer." CLINICAL IMMUNOLOGY (ORLANDO), vol. 91, no. 2, May 1999 (1999-05), pages 178-187, XP001042307 ISSN: 1521-6616 abstract figures table 1 page 184, right-hand column, paragraph DISCUSSION -page 185 ---	1-37
Y	GRANVILLE DAVID J ET AL: "Photodynamic treatment with benzoporphyrin derivative monoacid ring A produces protein tyrosine phosphorylation events and DNA fragmentation in murine P815 cells." PHOTOCHEMISTRY AND PHOTOBIOLOGY, vol. 67, no. 3, March 1998 (1998-03), pages 358-362, XP001042337 ISSN: 0031-8655 abstract page 361, paragraph DISCUSSION -page 362 ---	1-37
Y	SAVELLANO M D ET AL: "Pegylated BPD verteporfin C225 anti-EGF receptor direct covalent linkage photosensitizer immunoconjugates." PHOTOCHEMISTRY AND PHOTOBIOLOGY, vol. 69, no. SPEC. ISSUE., June 1999 (1999-06), page 38S, abstract MPM-E8, XP001042336 & Twenty Seventh Annual Meeting of the American Society for Photobiology; Washington, D.C., USA: July 10-15, 1999 ISSN: 0031-8655 abstract --- -/--	1-37



## INTERNATIONAL SEARCH REPORT

International Application No

PC1/US 01/00922

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	SCHMIDT-ERFURTH U ET AL: "PHOTODYNAMIC THERAPY OF SUBFOVEAL CHOROIDAL NEOVASCULARIZATION: CLINICAL AND ANGIOGRAPHIC EXAMPLES" GRAEFE'S ARCHIVE FOR CLINICAL AND EXPERIMENTAL OPHTHALMOLOGY, SPRINGER VERLAG, XX, vol. 236, no. 5, May 1998 (1998-05), pages 365-374, XP000853977 ISSN: 0721-832X abstract page 366, paragraph INTRODUCTION page 367, paragraph page 372, paragraph DISCUSSION -page 373 ---	1-37
Y	MARCUS S L: "PHOTODYNAMIC THERAPY OF HUMAN CANCER" PROCEEDINGS OF THE IEEE, IEEE. NEW YORK, US, vol. 80, no. 6, 1 June 1992 (1992-06-01), pages 869-889, XP000311053 ISSN: 0018-9219 page 883, right-hand column, paragraph XI -page 884, right-hand column ---	1-37
Y	JIANG F N ET AL: "ENHANCED PHOTODYNAMIC KILLING OF TARGET CELLS BY EITHER MONOCLONAL ANTIBODY OR LOW DENSITY LIPOPROTEIN MEDIATED DELIVERY SYSTEMS" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 19, no. 1 / 3, 1 March 1992 (1992-03-01), pages 41-58, XP000261528 ISSN: 0168-3659 abstract ---	1-37
Y	MEW D ET AL: "PHOTOIMMUNOTHERAPY: TREATMENT OF ANIMAL TUMORS WITH TUMOR-SPECIFIC MONOCLONAL ANTIBODY-HEMATOPORPHYRIN CONJUGATES" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 130, no. 3, 1 March 1983 (1983-03-01), pages 1473-1477, XP002048136 ISSN: 0022-1767 abstract page 1473 --- -/--	1-37

## INTERNATIONAL SEARCH REPORT

International Application No  
PC1/US 01/00922

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	<p>STERNBERG E D ET AL: "Porphyrin-based Photosensitizers for Use in Photodynamic Therapy" TETRAEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 17, 23 April 1998 (1998-04-23), pages 4151-4202, XP004113291 ISSN: 0040-4020 page 1487 -page 1491</p> <p>---</p>	1-37
Y	<p>WO 98 47541 A (COCKBAIN JULIAN R M ;KLAVENESS JO (NO); NAEVESTAD ANNE (NO); NYCOM) 29 October 1998 (1998-10-29) page 92, line 5 - line 19 examples 6,7</p> <p>---</p>	1-37
Y	<p>MARGARON PHILIPPE ET AL: "Photodynamic therapy inhibits cell adhesion without altering integrin expression." BIOCHIMICA ET BIOPHYSICA ACTA, vol. 1359, no. 3, 12 December 1997 (1997-12-12), pages 200-210, XP001042296 ISSN: 0006-3002 abstract figures</p> <p>-----</p>	1-37

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-37 in part

methods and kits as claimed, in which the photoactive compound is targeted using an antibody against the ED-B of fibronectin

2. Claims: 1-37 in part

methods and kits as claimed, in which the photoactive compound is targeted using VEGF

3. Claims: 1-37 in part

methods and kits as claimed, in which the photoactive compound is targeted using an antibody against integrin  $\alpha$ hpa-v,  $\beta$ 3

4. Claims: 1-37 in part

methods and kits as claimed, in which the photoactive compound is targeted using a combination of an antibody against CEA and an antibody against integrin  $\alpha$ hpa-v,  $\beta$ 3

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-37 in part

Present claims 1-37 relate to a method (claims 1-27) or a kit (claims 28-37), in which the definition of the photosensitising compound encompasses an extremely large number of possibilities. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Moreover, the definition of some specific ligands, as mentioned in claims 13, 27 and 31, does not correspond to the targeting moieties as used in the claims.

Also, in none of the claims, the photoactive compound is fully defined. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the photoactive compounds as used in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/00922

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9606641	A	07-03-1996	AU 3374795 A	22-03-1996
			WO 9606641 A1	07-03-1996
			US 6037329 A	14-03-2000
			AU 3724495 A	29-03-1996
			AU 710309 B2	16-09-1999
			AU 5862896 A	29-11-1996
			CA 2221269 A1	21-11-1996
			EP 0833665 A1	08-04-1998
			JP 11505805 T	25-05-1999
			WO 9608274 A2	21-03-1996
			WO 9636362 A1	21-11-1996
US 5929105	A	27-07-1999	US 6153639 A	28-11-2000
			AU 7420798 A	27-11-1998
			WO 9850387 A1	12-11-1998
			CN 1254339 T	24-05-2000
			EP 0983273 A1	08-03-2000
			HU 0003604 A2	28-02-2001
			JP 2001507369 T	05-06-2001
			NO 995436 A	04-01-2000
			PL 336790 A1	17-07-2000
US 5798349	A	25-08-1998	US 5707986 A	13-01-1998
			US 6225303 B1	01-05-2001
			US 2001023247 A1	20-09-2001
WO 9850387	A	12-11-1998	AU 7420798 A	27-11-1998
			WO 9850387 A1	12-11-1998
			CN 1254339 T	24-05-2000
			EP 0983273 A1	08-03-2000
			HU 0003604 A2	28-02-2001
			JP 2001507369 T	05-06-2001
			NO 995436 A	04-01-2000
			PL 336790 A1	17-07-2000
			US 5929105 A	27-07-1999
			US 6153639 A	28-11-2000
WO 9847541	A	29-10-1998	AU 733477 B2	17-05-2001
			AU 4718297 A	22-05-1998
			AU 733495 B2	17-05-2001
			AU 4786697 A	22-05-1998
			AU 4786797 A	22-05-1998
			AU 4787097 A	22-05-1998
			AU 7068798 A	13-11-1998
			BG 103438 A	31-01-2000
			BG 103439 A	31-01-2000
			BR 9712683 A	19-10-1999
			BR 9713978 A	02-05-2000
			CN 1238700 A	15-12-1999
			CN 1234742 A	10-11-1999
			CZ 9901494 A3	15-09-1999
			EP 1007101 A2	14-06-2000
			EP 0973552 A2	26-01-2000
			EP 0991427 A2	12-04-2000
			EP 0963209 A2	15-12-1999
			EP 0977600 A2	09-02-2000
			WO 9818500 A2	07-05-1998
			WO 9818501 A2	07-05-1998

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/00922

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9847541	A	WO 9818495 A2	07-05-1998
		WO 9818498 A2	07-05-1998
		WO 9847541 A1	29-10-1998
		HU 0000357 A2	28-06-2000
		JP 2001511765 T	14-08-2001
		JP 2001503407 T	13-03-2001
		JP 2001502719 T	27-02-2001
		NO 991889 A	28-06-1999
		NO 991890 A	28-06-1999
		US 6264917 B1	24-07-2001
		US 6331289 B1	18-12-2001
		US 6261537 B1	17-07-2001